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Original Article

Clinical and urodynamic effects of tolterodine in women with an overactive bladder

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Abstract

Objective: The aim of this study was to compare the changes in urinary symptoms and urodynamic parameters after administration of tolterodine in women with an overactive bladder (OAB).
Materials and Methods: Thirty-eight women diagnosed with OAB and treated with tolterodine were reviewed. Urinalysis, pelvic examination, 3-day bladder diary, urodynamic study, and a personal interview to identify urinary symptoms prior to and 3 months after treatment were recorded and interpreted.
Results: Most of our patients were menopausal (76.3%; mean age 55.7 years) and multiparous (mean parity 3.3) women. Urinary symptoms such as urinary frequency, urgency, urge incontinence, and nocturia were decreased significantly ($p < 0.05$). All urodynamic parameters did not change significantly except for the maximum cystometric capacity ($p < 0.05$), showing a significant increase after 3 months of medication.
Conclusions: Tolterodine, at a recommended dose, improves the symptoms of OAB syndrome without causing urine retention, as proved by the changes of urodynamic parameters.

Keywords: overactive bladder; tolterodine; urodynamic study

Introduction

Overactive bladder (OAB) is a common chronic problem that often requires long-term treatment to maintain control of symptoms. OAB, as defined by the International Continence Society, is a symptomatic diagnosis with urgency as the cornerstone symptom, with or without urge incontinence, but usually with urinary frequency and nocturia, in the absence of other pathological or metabolic factors that may otherwise cause similar symptoms [1]. OAB is a prevalent condition that can affect all aspects of quality of life. Suffering individuals have significant impairment of physical, social, emotional, and sexual functions [2,3].

The age-adjusted prevalence of OAB is around 17% in Taiwan as well as in the United States [4,5]. The prevalence of OAB increases with age in both sexes and occurs in approximately 30% in women over the age of 65 years [5]. The pathophysiology is not yet understood fully and is thought to be multifactorial. Nonsurgical treatment is the mainstay of therapy for OAB, including biofeedback, bladder training, electrical nerve stimulation, and medical treatment, or a combination of these methods.

Antimuscarinic agents are the first-line medical treatment for OAB symptoms and exert their effects on OAB by blocking the muscarinic receptors on most structures in the bladder wall (urothelium, lamina propria, and detrusor muscle) [6]. Various antimuscarinic agents appear to have different

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effects and side effects [7]. Of these agents, tolterodine and oxybutynin are used more commonly. Tolterodine is a newer drug designed specifically for treating OAB and has a relatively lower incidence of side effects [8].

Several reports had demonstrated the efficacy and safety of tolterodine in the treatment of OAB [7,8]. However, studies concerning the changes in urodynamic parameters and clinical symptoms after OAB treatment are limited [9,10]. Thus, the purpose of this study was to investigate the changes of urodynamic parameters and urinary symptoms after tolterodine treatment in female OAB patients.

Materials and methods

Between November 2005 and March 2007, 47 consecutive women visiting our outpatient clinic who underwent tolterodine (Detrusitol, Pfizer Inc., New York, USA) treatment for OAB were reviewed retrospectively. The changes of urodynamic parameters and subjective urinary symptoms after 3 months of treatment, as well as the demographic characteristics, were collected and compared. Nine patients were excluded from the study due to loss to follow-up, and incomplete or uninterpretable data.

During the first visit, detailed personal history, pelvic examination, and urinalysis were performed. A personal interview was also conducted for each woman with an OAB V8 questionnaire in order to identify the subjective urinary symptoms. A scale of 0–5 (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = a great deal, and 5 = a very great deal) [11] was used to record the incidences of subjective urinary symptoms. The diagnosis of OAB was made when the patient answered "somewhat" or more to any one of the three urge questions in the questionnaire (question 2, an uncomfortable urge to urinate; question 3, a sudden urge to urinate with little or no warning; question 7, an uncontrollable urge to urinate). In our recent report, translation of the OAB V8 questionnaire to Taiwanese has been validated for linguistic accuracy [12]. Any obvious etiology (such as pregnancy, genital organ prolapse, urinary tract infection, and any other diseases or medications that possibly affect the lower urinary tract functions) was excluded prior to the diagnosis of OAB.

All patients underwent a multichannel urodynamic study prior to treatment according to a fixed protocol; this evaluation was performed by the same experienced technician. The urodynamic study was performed with a six-channel urodynamic monitor (MMS; UD2000, Enschede, The Netherlands) according to the recommendations by the International Continence Society [13]. The studies included spontaneous uroflowmetry, both filling (at a rate of 50 mL/min with a 10F Foley catheter) and voiding cystometry with infusion of normal saline at room temperature, and urethral pressure profilometry. Any uninhibited detrusor contraction during filling cystometry was deemed positive for idiopathic detrusor overactivity (DO).

Patients who were diagnosed with OAB were given antimuscarinic therapy with tolterodine (2 mg bid) for 3 months. Post-treatment urodynamic study was then performed and interpreted by the same observer to avoid any interobserver bias; all patients were also asked to complete the questionnaire again. All the data of urodynamic study and the OAB V8 questionnaire after 3 months of tolterodine treatment were collected. Finally, nine women were excluded from the study due to incomplete medical records or loss to follow-up.

This study protocol was reviewed and approved by the Institutional Ethics Committee of our hospital. A statistical analysis was performed using the paired t test for continuous variables, and the McNemar or Chi-square test for categorical variables. A difference was considered statistically significant when $p < 0.05$.

Results

A total of 38 patients with complete data were included in this study. Demographic characteristics of all patients are shown in Table 1. The mean age was 55.7 years and mean body mass index was 25.6. Twenty-nine of the 38 women (76.3%) were menopaused and six (15.8%) were receiving hormone replacement therapy.

Subjective changes of urinary symptoms are shown in Table 2. Urinary symptoms, including urinary frequency, urgency, nocturia, and urge incontinence, were improved significantly after treatment ($p < 0.05$). The percentage of incomplete bladder emptying was increased nonsignificant. The number of episodes of stress urinary incontinence and urinary hesitancy did not differ significantly after treatment ($p > 0.05$).

Comparisons of the urodynamic parameters prior to and after treatment are shown in Table 3. Urodynamic stress incontinence, maximum detrusor pressure, maximum flow rate, residual urine, first sensation to void, detrusor pressure at peak flow, functional urethral length, and maximum urethral closure pressure did not differ significantly ($p > 0.05$), comparing all patients prior to and after the 3-month treatment of tolterodine. The rate of DO decreased but did not reach a significant difference ($p = 0.16$). Only the maximum cystometric capacity increased in a significant manner ($p = 0.04$). Seven patients had residual urine >100 mL after treatment.

Comparisons of the subjective changes of urinary symptoms between DO and non-DO patients are shown in Table 4. The

Table 1
Demographic characteristics of women (n = 38) with overactive bladder symptoms.

Mean age (years)	55.7 ± 11.4
Mean parity	3.3 ± 1.4
Mean BMI (kg/m^2)	25.6 ± 3.4
Menopause	29 (76.3)
Hormone therapy	6 (15.8)
Current smokers	5 (13.2)
Diabetes mellitus	5 (13.2)
Hypertension	11 (28.9)
History of hysterectomy	6 (15.8)

Data are presented as mean ± SD or n (%).
BMI = body mass index; POP = pelvic organ prolapse; SUI = stress urinary incontinence; Sx = surgery.

Table 2
Urinary symptoms prior to and after 3 months of medication.

Symptoms	Pre-Tx ($n = 38$)	Post-Tx ($n = 38$)	p value*
Urinary frequency	38 (100)	15 (39.5)	<0.01
Urgency	38 (100)	26 (68.4)	<0.05
Stress urinary incontinence	32 (84.2)	29 (76.3)	NS
Urge incontinence	24 (63.2)	14 (36.8)	<0.05
Incomplete bladder emptying	11 (29.0)	13 (34.2)	NS
Urinary hesitancy	3 (7.9)	2 (5.3)	NS
Nocturia	29 (76.3)	15 (39.5)	<0.05

Data are presented as n (%).
* McNemar's test.
Tx = treatment; NS = not significant.

subjective symptoms of urinary frequency were improved significantly in both groups. Moreover, the symptoms of urgency and nocturia were also improved in both groups; however, improvement in the symptom of urgency reached significance only in the DO group and that of nocturia only in the non-DO group. All the remaining symptoms were also decreased nonsignificantly except for the symptom of incomplete bladder emptying, which was increased nonsignificantly in the DO group and did not change in the non-DO group.

Discussion

Demographic data showed that the majority of our patients were of advanced age (mean age 55.7 years), postmenopausal (76.3%), and of greater parity (mean parity 3.3). These are compatible with the etiologic risk factors of OAB in Taiwanese women [14].

The subjective symptoms of urinary frequency, urge incontinence, and nocturia improved significantly ($p < 0.05$), but the numbers of episodes of stress urinary incontinence,

Table 3
Urodynamic changes prior to and after 3 months of medication.

	Pre-Tx ($n = 38$)	Post-Tx ($n = 38$)	p value
Parameters			
DO	18 (47.4)	15 (39.5)	>0.05*
USI	26 (68.4)	24 (63.2)	>0.05*
Qmax (mL/s)	19.7 ± 8.6	19.9 ± 12.4	>0.05**
RU (mL)	65.8 ± 35.4	77.5 ± 31.9	>0.05**
FS (mL)	145.1 ± 74.4	147.3 ± 80.9	>0.05**
MCC (mL)	311.1 ± 140.0	354.2 ± 122.2	<0.05**
Pdet (cmH_2O)	26.7 ± 17.7	26.0 ± 16.8	>0.05**
MDP (cmH_2O)	32.9 ± 18.8	31.2 ± 16.0	>0.05**
FUL (mm)	29.9 ± 11.9	29.7 ± 9.2	>0.05**
MUCP (cmH_2O)	83.5 ± 32.7	80.1 ± 28.6	>0.05**
UCA ($mm.cmH_2O$)	136.8 ± 69.5	127.5 ± 55.2	>0.05**

Data are presented as mean ± SD or n (%).
*McNemar's test.
**Paired t test.
DO = detrusor overactivity; FS = first sensation to void; FUL = functional urethral length; MCC = maximum cystometric capacity; MDP = maximum detrusor pressure; MUCP = maximum urethral closure pressure; Pdet = detrusor pressure at peak flow; Qmax = maximum flow rate; RU = residual urine; Tx = treatment; UCA = urethra; closure; USI = urodynamic stress incontinence.

Table 4
Urinary symptoms in women with and without DO prior to and after 3 months of medication.

	DO ($n = 18$)			No DO ($n = 20$)		
Symptoms	Pre-Tx	Post-Tx	p value*	Pre-Tx	Post-Tx	p value*
Urinary frequency	18 (100)	8 (44.4)	<0.05	20 (100)	7 (35.0)	<0.01
Urgency	18 (100)	10 (55.6)	<0.05	20 (100)	16 (80.0)	>0.05
SUI	17 (94.4)	15 (83.3)	>0.05	15 (75.0)	14 (70.0)	>0.05
Urge incontinence	12 (66.7)	7 (38.9)	>0.05	12 (60.0)	7 (35.0)	>0.0.5
Incomplete emptying	4 (22.2)	6 (33.3)	>0.05	7 (35.0)	7 (35.0)	>0.05
Urinary hesitancy	1 (5.6)	1 (5.6)	>0.05	2 (10.0)	1 (5.0)	>0.05
Nocturia	11 (61.1)	7 (38.9)	>0.05	18 (90.0)	8 (40.0)	<0.01

* McNemar's test.
Data are given as n (%).
DO = detrusor overactivity; SUI = stress urinary incontinence; Tx = treatment.

incomplete bladder emptying, and urinary hesitancy did not differ significantly after treatment. These results reflected the pharmacologic effect of anticholinergic agents, taking into account its small impact on stress urinary incontinence. The symptom of urgency was improved nonsignificantly, which may be attributed to the limited number of patients included in the study.

The common view of the action of tolterodine in OAB patients is that it acts by blocking competitively the muscarinic receptors on the detrusor muscle, which are stimulated by acetylcholine released from activated parasympathetic nerves. As a result, it inhibits the contractile ability of the bladder. This blocking activity occurs mainly during the storage phase of the bladder, increasing the total bladder capacity [15]. Several studies have shown a significant increase in the bladder capacity after anticholinergic medication [9,10]. Therefore, the maximum bladder capacity has been suggested to be a useful marker of the efficacy of treatment [16]. In this study, a similar result was obtained, indicating the efficacy of tolterodine in the treatment of OAB.

As mentioned above, tolterodine is a competitive antagonist against muscarinic receptors; hence, although the concentration of acetylcholine is increased massively during the voiding phase, the effect of tolterodine may be reduced. As expected, no statistically significant changes were found in the urodynamic parameters of voiding function, including maximum flow rate, maximum detrusor pressure, and detrusor pressure at peak flow.

Undoubtedly, blocking the contraction of the bladder may also decrease the power of voiding and cause urine retention. In our study, the mean volume of residual urine was increased nonsignificantly ($p = 0.33$) after treatment. Seven patients had residual urine >100 mL after treatment. Other authors also reported similar results, showing no significant change in residual urine [9,10]. Therefore, the concern that tolterodine may increase the risk of urine retention can be ignored in cases of short-term use at normal dosage. Moreover, during this study, no significant changes were observed in the maximum

flow rate, maximum detrusor pressure, and detrusor pressure at peak flow. Hsiao et al [17,18] also reported similar findings. According to the above findings, tolterodine may not cause clinically significant deterioration of voiding function, but more attention should be paid to those women with large residual urine volume prior to treatment.

The rate of DO decreased nonsignificantly after treatment (47.4% vs. 39.5%, $p = 0.16$). Up to 50% of asymptomatic women showed DO during ambulatory tests [19], which is similar to our study. The detection rate of DO by urodynamic study varies greatly, because a number of factors, including the posture of the patient during the test, type of infusion medium used, temperature of the medium, rate of infusion, and provocative tests used, cause detrusor contraction [20]. Thus, the percentage of DO may not be a good predictor to evaluate the efficacy of treatments, especially when the procedures of urodynamic study were not standardized.

In general, the subjective urinary symptoms, including urinary frequency, urgency, stress urinary incontinence, urge incontinence, and nocturia, were improved. If we divide all the patients into DO and non-DO groups, tolterodine was found to be effective in improving the symptoms of frequency in both groups, but it had greater impact on urgency in the DO group. In addition, there was no change in urinary hesitancy and a nonsignificant increase of incomplete bladder emptying in the DO group, but no change in the non-DO group. Therefore, tolterodine is not related to the deterioration of voiding function. As mentioned above, the detection rate of DO by urodynamic study may not be a good predictor to evaluate the efficacy of treatments. Moreover, the limited number of patients enrolled may also cause bias.

The main limitation of this study is the small size of study samples. Moreover, over 70% of patients had stress urinary incontinence symptoms, indicating that most of the patients in this study had mixed urinary incontinence, which may also be a factor of influence. By contrast, a fixed protocol of urodynamic examination, performed by the same experienced technician and interpreted by the same observer, can avoid any interobserver bias. Moreover, completion of the entire questionnaire by the patients themselves also minimized the bias from other persons' opinions.

Results of our study suggested that tolterodine improves the symptoms of frequency, nocturia, and urge incontinence in female OAB patients. Lack of changes in the urodynamic parameters also revealed that anticholinergic agents had no adverse effect on the voiding function. Moreover, a greater impact on the therapeutic effects was observed in DO patients. In conclusion, tolterodine, at a recommended dosage, is an effective antimuscarinic agent for women with OAB, without causing urinary retention.

References

[1] Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology 2003 Jan;61(1):37–49.

[2] Wagner TH, Hu TW, Bentkover J, LeBlanc K, Stewart W, Corey R, et al. Health-related consequences of overactive bladder. Am J Manag Care 2002 Dec;8(19 Suppl.):S598–607.

[3] Coyne KS, Sexton CC, Irwin DE, Kopp ZS, Kelleher CJ, Milsom I. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. BJU Int 2008 Jun;101(11):1388–95. http://dx.doi.org/10.1111/j.1464-410X.2008.07601.x.

[4] Yu HJ, Liu CY, Lee KL, Lee WC, Chen TH. Overactive bladder syndrome among community-dwelling adults in Taiwan: prevalence, correlates, perception, and treatment seeking. Urol Int 2006;77(4):327–33.

[5] Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, et al. Prevalence and burden of overactive bladder in the United States. World J Urol 2003 May;20(6):327–36 [Epub 2002 Nov 15].

[6] Moro C, Uchiyama J, Chess-Williams R. Urothelial/lamina propria spontaneous activity and the role of M3 muscarinic receptors in mediating rate responses to stretch and carbachol. Urology 2011;78. 1442.e9–15.

[7] Novara G, Galfano A, Secco S, D'Elia C, Cavalleri S, Ficarra V, et al. A systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. Eur Urol 2008 Oct;54(4):740–63.

[8] Malone-Lee J, Shaffu B, Anand C, Powell C. Tolterodine: superior tolerability than and comparable efficacy to oxybutynin in individuals 50 years old or older with overactive bladder: a randomized controlled trial. J Urol 2001 May;165(5):1452–6.

[9] Jonas U, Höfner K, Madersbacher H, Holmdahl TH. Efficacy and safety of two doses of tolterodine versus placebo in patients with detrusor overactivity and symptoms of frequency, urge incontinence, and urgency: urodynamic evaluation. The International Study Group. World J Urol 1997;15(2):144–51.

[10] Wagg A, Malone-Lee J. Pressure-flow variables in patients treated with tolterodine for detrusor overactivity. BJU Int 2003;92:969–71.

[11] Acquadro C, Kopp Z, Coyne KS, Corcos J, Tubaro A, Choo MS, et al. Translating overactive bladder questionnaires in 14 languages. Urology 2006 Mar;67(3):536–40.

[12] Long CY, Hsu CS, Wu MP, Liu CM, Chiang PH, Juan YS, et al. Predictors of improved overactive bladder symptoms after transvaginal mesh repair for the treatment of pelvic organ prolapse: predictors of improved OAB after POP repair. Int Urogynecol J 2011;22:535–42.

[13] Abrams P, Blaivas JG, Stanton SL, Andersen JT. The standardisation of terminology of lower urinary tract function. The International Continence Society Committee on Standardisation of Terminology. Scand J Urol Nephrol Suppl 1988;114:5–19.

[14] Chen GD, Lin TL, Hu SW, Chen YC, Lin LY. Prevalence and correlation of urinary incontinence and overactive bladder in Taiwanese women. Neurourol Urodyn 2003;22(2):109–17.

[15] Andersson KE. Antimuscarinics for treatment of overactive bladder. Lancet Neurol 2004;3:46–53.

[16] Colli E, Parazzini F, Olivieri L, Cipriani S, Bertozzi R, Meschia M, et al. Number of daytime micturitions and volume voided per micturition in the evaluation of efficacy of drugs for overactive bladder: findings from randomized clinical trials. Eur Urol 2007 Aug;52(2):525–30. [Epub 2007 Apr 2]. Review.

[17] Hsiao SM, Chang TC, Wu WY, Chen CH, Yu HJ, Lin HH. Comparisons of urodynamic effects, therapeutic efficacy and safety of solifenacin versus tolterodine for female overactive bladder syndrome. J Obstet Gynaecol Res 2011;37:1084–91.

[18] Wu WY, Hsiao SM, Chang TC, Lin HH. Changes in urodynamic parameters after tolterodine treatment for female overactive bladder syndrome with or without voiding dysfunction. J Obstet Gynaecol Res 2011;37:436–41.

[19] Heslington K, Hilton P. Ambulatory monitoring and conventional cystometry in asymptomatic female volunteers. Br J Obstet Gynaecol 1996;103:434–41.

[20] Al-Hayek S, Belal M, Abrams P. Does the patient's position influence the detection of detrusor overactivity? Neurourol Urodyn 2008;27:279–86.